CHAPTER I - INTRODUCTION
Sutter-Kostic and Karrer\textsuperscript{1} were the first to observe the disproportionation of N-methyl-1,2-dihydroquinoline \textsuperscript{1} in the presence of ethanolic hydrogen chloride. 1-Phenylisoquinoline \textsuperscript{2} and 1-phenyl-1,2,3,4-tetrahydroisoquinoline \textsuperscript{2} have been obtained by distillation of 1-phenyl-3,4-dihydroisoquinoline \textsuperscript{4}. \textsuperscript{2} \textsuperscript{4}-(\beta\textsuperscript{-}Phenylethylamino)-1,2,3,4-tetrahydroquinoline \textsuperscript{5} and the corresponding quinoline are formed by the interaction of \beta\textsuperscript{-}phenylethylamine and 4-keto-1,2,3,4-tetrahydroquinoline \textsuperscript{6} with ammonium chloride and zinc chloride\textsuperscript{3}. This reaction probably involves intermediate formation of \textsuperscript{4}-(\beta\textsuperscript{-}phenylethylamino)-1,2-dihydroquinoline \textsuperscript{7}. The synthesis of lepidine and its derivatives, starting from \beta\textsuperscript{-}arylaminoethyl ketones, in the presence of oxidising agents and acids has been reported\textsuperscript{4}.

The acid-catalysed cyclodehydration of alkyl/aryl \beta\textsuperscript{-}aminoethyl ketones and disproportionation of the intermediate 1,2-dihydroquinolines leading to formation of tetrahydroquinolines and quinolines has been studied by Tilak et al.\textsuperscript{5,6} in greater detail.\textsuperscript{5,6} The mechanism of the formation of quinolines and tetrahydroquinolines from 1,2-dihydroquinoline and its precursors such as alkyl/aryl \beta\textsuperscript{-}aminoethyl ketones is analogous to the acid-catalysed disproportionation of \textsuperscript{7,8}3\textsuperscript{-}thiachromens\textsuperscript{7,8} and \textsuperscript{3}\textsuperscript{-}chromenes\textsuperscript{9}. The disproportionation
involves an intermolecular hydride transfer between one molecule of dihydroquinolines acting as hydride donor and another molecule of the same in its protonated form as a hydride acceptor.

The above cyclodehydration reaction yields exclusively quinolines when triphenylmethylchloride is used as an external hydride abstractor. For example, methyl \( \beta \)-(phenylaminoethyl) ketone on treatment with polyphosphoric acid gave a mixture of 4-methylquinoline and 4-methyl-1,2,3,4-tetrahydroquinoline along with traces of 4-methyl-1,2-dihydroquinoline. Methyl 2-(\( \beta \)-naphthylamino)-ethyl ketone prepared by condensation of \( \beta \)-naphthylamine and 1-diethylamino-3-butanone hydrochloride gave on cyclisation with ethanolic HCl a mixture of 4-methylbenzo[f]quinoline and 4-methyl-1,2,3,4-tetrahydrobenzo[f]quinoline. 2-(Dimethylaminoethyl)-cyclohexanone hydrochloride was condensed with m-anisidine, \( \beta \)-naphthylamine and \( \alpha \)-naphthylamine to give the \( \beta \)-arylaminomethylcyclohexanones respectively. Compound on cyclisation with PPA in the presence of triphenylmethyl chloride gave 8-methoxy-1,2,3,4-tetrahydrobenzo[c]quinoline. Compound on treatment with PPA alone gave a mixture of 1,2,3,4,4a,5,6,12c-octahydrobenzo[a]phenanthridine and 1,2,3,4-tetrahydrobenzo[a]phenanthridine. However, when was reacted with PPA in the presence of triphenylmethylchloride a
molecular complex 24 of 23 with triphenyl carbinol was obtained. Compound 23 was isolated from 24 by interaction with dil. HCl and basification of the acidic solution. Compound 23 was characterised by its conversion to the methiodide 25. Selenium dehydrogenation of 23 gave benzo[a]phenanthridine 26.

2-(α-Naphthylamino)-methylcyclohexanone 27 on interaction with PPA gave back α-naphthylamine by a retro-Michael reaction. However, when 27 was treated with boiling ethanolic HCl, 1,2,3,4-tetrahydrobenzo[c]phenanthridine 28 and 1,2,3,4,4a,5,6,12b-octahydrobenzo[c]phenanthridine 29 were obtained in addition to α-naphthylamine. Compound 28 on dehydrogenation with selenium gave benzo[c]phenanthridine 30 (Chart 1).

Tilak et al.13 were interested in the synthesis of quinoline derivatives which would not involve disproportionation observed in the above synthesis. A good approach for realizing this objective appeared to be the cyclodehydration of 2-arylaminoalkenones. Literature survey revealed that Borche14 has reported the synthesis of 2-phenylaminomethylene cyclohexanone 31a but his attempts to cyclise it were unsuccessful. The failure was attributed to the trans structure for this 'anil' 34 15 (Chart 2). However, when 31a was treated either with P2O5 or POCl3, 1,2,3,4-tetrahydroacridine 33a was formed16. Petrow15 took
31

32

33

34

35 \( x = \text{OH} \)

36 \( x = O - \text{SO}_2 - \text{C}_6\text{H}_4 - \text{CH}_3 \)

a, \( R = 7' - \text{OCH}_3 \)
b, \( R = 7' - \text{Cl} \)
c, \( R = 8' - \text{CH}_3 \)
d, \( R = 9' - \text{OCH}_3 \)

u, \( R = \text{H} \)
v, \( R = 5' - \text{OCH}_3 \)
w, \( R = 6' - \text{CH}_3 \)
x, \( R = 6 - \text{OCH}_3 \)
y, \( R = 6 - \text{Cl} \)
z, \( R = 7' - \text{CH}_3 \)
g, \( R = 7' - \text{OH} \)

\( R_1 \) and
\( R_2 = \text{H}, \text{CH}_3, -\text{OCH}_3, \text{Cl} \)

CHART - 2
for granted the anil structure for the reaction product formed by the interaction of aniline and cis-2-hydroxymethylene cyclohexanone and cyclised this product to 23a by treatment with aniline hydrochloride as such or in ethanolic solution with an optional addition of zinc chloride. In terms of Petrow's mechanism (Chart 3) ring closure of the arylaminomethylene ketone 27 in the presence of amine hydrochloride occurs through reaction of the second molecule of amine with the remaining carbonyl group in the starting material with final extrusion of the amine residue originally present after the ring closure.

To define the scope, limitations and to elucidate the mechanism of cyclodehydration of arylaminomethylene alkanones, Tilak et al.\textsuperscript{13} cyclodehydrated cis-2(3'-methoxyphenylaminomethylene)cyclohexanone 31d by treatment with PPA when 7-methoxy-1,2,3,4-tetrahydrophenanthridine 32a (96% yield) was obtained. When 2-(1'-naphthylaminomethylene)cyclohexanone 41 and 2-(2'-naphthylaminomethylene)cyclohexanone 43 were treated with PPA gave 1,2,3,4-tetrahydrobenzo[c]phenanthridine 42 and 1,2,3,4-tetrahydrobenzo[a]phenanthridine 44. Cyclodehydration of cis-2(3'-methoxyphenylaminomethylene)-cyclopentanone 45 and cis-2-(3'-methoxyphenylaminomethylene)-cycloheptanone 48 by interaction with PPA gave 3,4-cyclopenteno-7-methoxyquinoline 46 and 3,4-cyclohepteno-7-methoxyquinoline 49.
Chart 3
respectively. In the above cyclisation of 45, in addition to 46, 3,4-cyclopenteno-5-methoxyquinoline 47 was also obtained (Chart 4).^{17}

However, cyclodehydration of cis-2-(3'-methoxyphenylaminomethylene)-cyclohexanone 31d by treatment with aniline hydrochloride/anhydrous ZnCl₂ in boiling ethanol gave 6-methoxy-1,2,3,4-tetrahydroacridine 33d (57%)^{13}.

Several cis-2-arylaminomethylene-cyclohexanones 31a-g were cyclodehydrated with different primary arylamine hydrochlorides in boiling ethanol in the presence of anhydrous zinc chloride to obtain tetrahydroacridines 33a-g, wherein the arylamine moiety present originally in 31 was retained (as in 33a) or substituted (as in 33b) by the interacting arylamine (used as hydrochloride).

The mechanism suggested by Tilak et al.\(^{13}\) postulates that the substitution of the arylamine \(R_1^{-C_6H_4-NH_2}\) used in cyclodehydration probably takes place through the implication of the intermediate 'dianil' 50 (Chart 5) (reaction following scheme A). The retention of original arylamine present in 31 in the final tetrahydroacridine 33a was explained on the assumption that the reaction follows an alternate path (scheme B, Chart 5). In latter case acid-catalysed substitution of \(R_1^{-C_6H_4-NH_2}\) present in 31 by \(R_2^{-C_6H_4-NH_2}\) occurs as a first step to yield 31a and then further reactions follow a sequence.
similar to scheme A whereby acridine 33a finally results in which arylamine moiety present in 31 is retained by a process of elimination and reincorporation. In scheme B acid-catalysed displacement of the arylamine present in 31 by the arylamine used for cyclodehydration has been envisaged, the reaction proceeding through the amine salt 51 derived from 31. The enamine salt 51 then reacts with the arylamine R_2-C_6H_4-NH_2 used for cyclodehydration and yields a new cis-2-arylaminomethylenecyclohexanone 31a. The latter then reacts further according to scheme A to finally yield 33a. The fact that the amine present in 31 interchanges with other amines (used as hydrochlorides), depending on the comparative basicity of the two amines was shown by carrying out the exchange and corresponding control reactions (Chart 5). 4-Methylcyclohexanone (D) on formylation yielded 2-aldehydo -4-methylcyclohexanone 52. The latter on interaction with aniline and m-anisidine yielded the corresponding enamines 53a and 53b. Cyclodehydration of the latter compounds respectively with aniline hydrochloride and m-anisidine hydrochloride gave 2-methyl-1,2,3,4-tetrahydroacridine 54a and 6-methoxy-2-methyl-1,2,3,4-tetrahydroacridine 54b. A mixture of 31a and 53b was then treated with aniline hydrochloride (2 moles) in boiling ethanol in the presence of ZnCl_2 (1 mole) whereby a mixture of 33a, 33d, 54a and 54b was formed. The formation of these compounds was explained on the basis
SCHEME A

SCHEME B

\[ R = H \]
\[ R = 3'-OCH_3 \]

33a (33%) 33a(15%) 54a (18%) 54b (34%)
of reactions outlined in Chart 5.

The concept of 'dianil' (either 38 in Chart 3 or 50 in Chart 5) as the probable intermediate has been recently substantiated. Thus Acheson et al. \(^\text{18}\) isolated the 'bis-anil' 57 from 55 in hot lactic acid. This showed that acid-catalysed reaction of 55 to 57 occurred probably via hydrolysis to the amine 56. Compound 57 was identical with an authentic specimen prepared from 2-chloro-cyclohexanol and 2-aminobiphenyl by the method of Gagen and Lloyd\(^\text{19}\). The bis-anil 57 with glacial acetic acid at 100° for 1 hr was completely converted to the acridine 56 and 2-aminobiphenyl, while the mono-anil 55 was unchanged under these conditions. The mono-anil 55 however, with anhydrous lactic acid (130° 20 hr) did give 58 (25%) and the \(N-(2\text{-diphenyl})\text{-lactamide (47%)}\) 59 (Chart 6).

Recently Hall and Walker observed\(^\text{20}\) that ring closure of 2-(1'-naphthylaminomethylene)cyclohexanone 41 in the presence of 2-naphthylamine hydrochloride gave a moderate yield of 1,2,3,4-tetrahydrobenz[a]acridine 60. But cyclodehydration of 41 by interaction with aniline hydrochloride and fused zinc chloride in boiling ethanol gave only 1,2,3,4-tetrahydrobenz[c]acridine 61 (50% yield). When the reaction was repeated by Tilak et al.\(^\text{17}\), they obtained in addition to 61 (55% yield), 1,2,3,4-tetrahydroacridine 33a (28% yield). However, similar cyclodehydration of cis-2(2'-naphthylaminomethylene)-cyclo-
hexanone 43 gave only 1,2,3,4-tetrahydrobenz[a]acridine 60 (yield 65%) (Chart 7).

For the cyclodehydrations of arylaminomethylene-cycloalkanones Hall and Walker have suggested a different reaction mechanism. The mechanism suggested by them envisages the protonation at the carbonyl group as in 62 or at the nitrogen atom as in 63. In the case of 62 ring closure would give the phenanthridine 42. In the case of 63 a rearrangement leading to linear tetrahydroacridine 61 was explained by assuming the addition of two molecules of the acid to the starting enamines 41, followed by cleavage of the -C(NH₂) bond and recombination of the fragments. In the latter process interaction of the o-position with respect to the amino group in the arylamine and the carbonium ion at carbon carrying the leaving group in the cyclohexanone fragment was envisaged (Chart 8).

This mechanism appears improbable because one might expect the p-position in the liberated arylamine fragment to be implicated in these reactions. Secondly, the arylamines react with compounds such as 2-hydroxy-methylenecyclohexanone 35 and cis-2-(4'-tosyloxy)methylene)cyclohexanone 36 to yield compounds 31 even under mild conditions, no cyclisations being noticed. Further, the addition of two moles of acid to the enamines 41 and 42 suggested by Hall and Walker appears improbable, since enamines such as 31 add only one mole of acid to give the
CHART - 8

CHART - 9
enamine salts 51.

Though suffering from these basic misconceptions as above some intermediates which appear to substantiate this mechanism are now reported by Tilak et al. 21. Condensation of 3-hydroxymethylene-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 64 with α-naphthylamine and β-naphthylamine gave cis-3-(1'-naphthylamine-methylene)-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 65 and cis-3-(2'-naphthylamine-methylene)-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 66. When 65 was heated with α-naphthylamine hydrochloride and fused zinc chloride in boiling ethanol gave trans-3-(1'-amino-2'-naphthylmethylene)-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 67. The other products of the reaction were α-naphthylamine and a lactum 68 (Chart 9). When 66 was heated with β-naphthylamine hydrochloride fused zinc chloride in boiling ethanol gave trans-3-(2'-amino-1'-naphthylmethylene)-N-methyl-1,2,3,4-tetrahydroquinoline-4-one 69. The other products of the reaction were β-naphthylamine and a lactum 70 (Chart 10). Both 67 and 69 were trans-oriented and therefore did not cyclise. The corresponding cis products 71 and 72 were also formed but they undergo spontaneous cyclisation leading eventually to 68 and 70, through steps shown in Charts 11 and 12. The formation of lactum 68 and 70 was explained on the basis of intermediates 73, 74, 75 and 76.
CHART - 12

CHART - 13
Hall and Walker had used lactic acid for their cyclodehydration reactions. Subsequently, Tilak et al. reported that when the cyclodehydration of 31 was effected by interaction with different arylamines in presence of lactic acid a mixture of acridines, 33a and 33b was obtained. Under milder conditions conversion of 31 to another cis-2-(arylamino)methylene-cyclohexanone 31a was also observed. When the cyclodehydration of 31c and 31g was carried out by heating with lactic acid 33c and 33g were obtained in 64 and 49% yield respectively. Interaction of 2-hydroxy-methylene-cyclopentanone with α-naphthylamine and β-naphthylamine gave cis-2-(1'-naphthylaminomethylene)-cyclopentanone 77 and cis-2(2'-naphthylaminomethylene)-cyclopentanone 79. Cyclodehydration of 77 and 79 by interaction with lactic acid yielded 4-aza-cyclopenteno[b]-phenanthrene 78 and 1-aza-cyclopenteno[b]phenanthrene 80 respectively. In cyclodehydration of 79, 80 and β-naphthylamine lactate 81 were formed in nearly equivalent quantities. Cyclodehydration of both 77 and 79 leads to linear heterocycles 78 and 80 by rearrangement, instead of the normal angular cyclodehydration products 82 and 83. (Chart 13).

It was interesting to investigate the role played by lactic acid as against acetic or propionic acids, in giving high yields of the rearranged acridines. Tilak et al. have suggested the sequence of reactions shown in Chart 14, which might be occurring during cyclodehydration of 31 when
lactic acid is used.

The anchimeric assistance afforded by the hydroxy group in (c) assists the elimination of arylamino group in 31 leading to 2(2'-keto-1'-cyclohexyl)-4 keto-5-methyl-1,3-dioxolone 84, which then reacts with the eliminated arylamine leading finally to an acridine 31a. Although it was not possible to isolate 84, it was separately prepared by the interaction of cis-2(4'-tosyloxy methylene)-cyclohexanone 36 with anhydrous calcium lactate. When 84 was treated with m-anisidine and lactic acid in boiling ethanol solution 31d (3%) and 33d (37%) were formed whereas its interaction with m-anisidine in boiling ethanol (in absence of lactic acid) gave 33d (43%) and 31d (57%).

Apart from isolation of 84, the concept of anchimeric assistance in case of lactic acid was substantiated, by the failure of propionic acid to effect the above cyclisation.

When the cyclodehydration of 41 and 43 was carried out by interaction with lactic acid 61 and 60 were obtained in 60% yield. When 2-(2'-keto-1'-cyclohexyl)-4-keto-5-methyl-1,3-dioxalane 84 was reacted with α-naphthylamine, compounds 41 and 61 were obtained in 13 and 41% yields. Similar reaction of 84 with β-naphthylamine yielded 43 and 60 in 9 and 68% yields respectively (Chart 15).

Cyclodehydration of the enaminoketone 31 by
interaction with just fused ZnCl₂ in boiling ethanol was also studied by Tilak et al. Under these conditions the enaminoketones 31d-f gave the corresponding tetrahydroacridines 33d-f in low yield (16-24%). For these reactions the mechanism shown in Chart 16 was suggested. The above scheme envisages the intermediate formation of the azetine salt (E) which then rearranges to finally yield 33a. Extended HMO calculations indicated the feasibility of existence of 'azetines' (P.T. Narasimhan, private communication). In these cases the leaving group (E) may be an arylamine or o-acyl group.

With a view to obtain tetrahydroquinoline in better yields, acid-catalysed cyclodehydration of 1-arylamino-3-alkanols was studied. Cyclodehydration of the alkanols 85, under acid conditions, yielded 3,4-disubstituted-1,2,3,4-tetrahydroquinoline 86, along with rearranged 2,3-disubstituted-1,2,3,4-tetrahydroquinolines 87 (Chart 17).

3-(3'-Methoxyphenylamino)-1-phenyl-1-propanol 88 on treatment with 70% sulphuric acid furnished 1-(3'-methoxyphenyl)-2-phenyl-azetidine 89 along with the rearranged product 7-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 90.

However, 3-phenylamino-1-phenyl-1-propanol 91 and 3-phenylamino-1-(2'-thienyl)-1-propanol 92 under similar
conditions yielded essentially the normal products, 4-phenyl-1,2,3,4-tetrahydroquinoline 23 and 4-(2'-thienyl)-1,2,3,4-tetrahydroquinoline 24 and the respective rearranged products 25 and 26 were obtained in very small amounts (Chart 18).

Cyclodehydration of 3-(3'-methoxyphenylamino)-2-methyl-1-phenyl-1-propanol 27 by treatment with 70% sulphuric acid led to a mixture of 7-methoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline 28 and the rearranged 7-methoxy-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 29 in 21 and 37% yield. Under similar conditions 2-methyl-3-phenylamino-1-propanol 100 and 1,2-diphenyl-3-phenylamino-1-propanol 101 yielded the rearranged products 3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 102 and 2,3-diphenyl-1,2,3,4-tetrahydroquinoline 103 respectively. In the former case a small quantity of 3-methyl-2-phenyl-1-phenyl-azetidine 104 was also isolated.

In an analogous manner 3-(3'-chloro-phenylamino)-1-(2'-thienyl)-1-propanol 105 on treatment with phosphorous pentoxide in tetrahydrofuran afforded a mixture of 7-chloro-4-(2'-thienyl)-1,2,3,4-tetrahydroquinoline 106, 7-chloro-2-(2'-thienyl)-1,2,3,4-tetrahydroquinoline 107 in which the former predominated 24.

In all the above cases the alkanols were prepared by the sodium borohydride reduction of either the corresponding
β-arylaminomethyl, alkyl/aryl ketones or cis-2-arylaminomethylene alkanones (108 to 114) (Chart 18).

The formation of 93, 94, 98 and 106 by the cyclo-dehydration of the relevant 3-arylamino-1-propanols was normally expected. However, the simultaneous formation of 90, 95, 96, 99, 102, 103 and 107 was rationalised on the basis of the involvement of an intermediate 1-arylazetidine which on ring expansion led to the two possible tetrahydroquinolines. Ring expansion of N-aryl azetidines (A) involves a suprafacial sigmatropic rearrangement with inversion at C₃-C₄ or C₂-C₃ bond in the azetidine. An analogous example in the carbocyclic series has been reported by Berson.

The present work was undertaken to throw more light on the above cyclodehydration reactions. To prove the mechanism shown in Chart 16, it was necessary to prepare N-arylazetidines and to rearrange them to acridines under acidic conditions. To prove the mechanism in Chart 17 it was necessary to prepare N-arylazetidines and to rearrange them into tetrahydroquinolines. Since N-arylazetidines appear to be susceptible to acid-catalysed rearrangement, it was necessary to develop methods to synthesise them preferably under neutral or alkaline conditions. Secondly, N-arylazetidines themselves may serve as starting materials for the synthesis of N-arylazetidines. Lastly it was of great interest to study the stereochemistry of N-arylazetidines.
\[ R_1 = \emptyset, R_2 = H, R_3 = OCH_3 \]
\[ R_1 = \emptyset, R_2 = R_3 = H \]
\[ R_1 = 2'-\text{thienyl}, R_2 = R_3 = H \]
\[ R_1 = \emptyset, R_2 = CH_3, R_3 = OCH_3 \]
\[ R_1 = \emptyset, R_2 = CH_3, R_3 = H \]
\[ R_1 = 2'-\text{thienyl}, R_2 = H, R_3 = Cl \]
\[ R_1 = \emptyset, R_2 = CH_3, R_3 = H \]
\[ R_1 = 2'-\text{thienyl}, R_2 = R_3 = H \]
\[ R_1 = \emptyset, R_2 = CH_3, R_3 = H \]
\[ R_1 = 2'-\text{thienyl}, R_2 = H, R_3 = Cl \]
\[ R_1 = \emptyset, R_2 = CH_3, R_3 = OCH_3 \]
\[ R_1 = 0, R_2 = CH_3, R_3 = H \]
\[ R_1 = R_2 = \emptyset, R_3 = H \]
and the tetrahydroquinolines derived therefrom and to see how the products fit in with Woodward and Hoffmann hypotheses of orbital symmetry.
REFERENCES


